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Original Article

The importance of polysomnography in the evaluation of prolonged disorders of consciousness: sleep recordings more adequately correlate than stimulus-related evoked potentials with patients' clinical status

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ABSTRACT

Objectives: The aim of our study was to evaluate the importance of sleep recordings and stimulus-related evoked potentials (EPs) in patients with prolonged disorders of consciousness (DOCs) by correlating neurophysiologic variables with clinical evaluation obtained using specific standardized scales.
Methods: There were 27 vegetative state (VS) and 5 minimally conscious state (MCS) patients who were evaluated from a clinical and neurophysiologic perspective. Clinical evaluation included the Coma Recovery Scale-Revised (CRS-R), Disability Rating Scale (DRS), and Glasgow Coma Scale (GCS). Neurophysiologic evaluation included 24-h polysomnography (PSG), somatosensory EPs (SEPs), brainstem auditory EPs (BAEPs), and visual EPs (VEPs).
Results: Patients with preservation of each single sleep element (sleep–wake cycle, sleep spindles, K-complexes, and rapid eye movement [REM] sleep) always showed better clinical scores compared to those who did not have preservation. Statistical significance was only achieved for REM sleep. In 7 patients PSG showed the presence of all considered sleep elements, and they had a CRS-R score of 8.29 ± 1.38. In contrast, 25 patients who lacked one or more of the sleep elements had a CRS-R score of 4.84 ± 1.46 ($P < .05$). Our multivariate analysis clarified that concurrent presence of sleep spindles and REM sleep were associated with a much higher CRS-R score (positive interaction, $P < .0001$). On the other hand, no significant associations were found between EPs and CRS-R scores.
Conclusions: PSG recordings have proved to be a reliable tool in the neurophysiologic assessment of patients with prolonged DOCs, correlating more adequately than EPs with the clinical evaluation and the level of consciousness. The main contribution to higher clinical scores was determined by the concomitant presence of REM sleep and sleep spindles. PSG recordings may be considered inexpensive, non-invasive, and easy-to-perform examinations to provide supplementary information in patients with prolonged DOCs.

1. Introduction

Due to advances in critical care, an increasing number of patients survive from an acute brain injury causing an increased incidence and prevalence of patients with disorders of consciousness (DOCs). Behavioral assessment currently is the main method used to detect signs of awareness in severely brain injured patients recovering from coma [1]. However, disentangling the vegetative state (VS) from the minimally conscious state (MCS) often is difficult when only relying on behavioral observation [2]. Clinical misdiagnosis is partly explained by the inherent difficulties in detecting signs of awareness in patients with fluctuating arousal and possible perceptual, attentional, cognitive, and motor deficits. Previous studies have shown that 37–43% of patients diagnosed with VS demonstrated signs of awareness [3,4].

The most commonly reported error is a false-negative diagnosis of a patient who is actually in MCS being misdiagnosed as VS. The JFK Coma Recovery Scale-Revised (CRS-R) is commonly considered

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the most reliable and validated scale for the standardized evaluation of patients with prolonged DOCs. The CRS-R was developed specifically to differentiate MCS from VS [5,6]. However, evaluating DOCs patients may be extremely challenging, even using standardized scales such as CRS-R. Neuroimaging and neurophysiologic techniques may be helpful to assess residual cerebral functions, which in turn could aid in differentiating between states in which consciousness is impaired [7]. Neurophysiologic assessment represents an option that provides valuable clinical insight while being more accessible than functional imaging modalities [8]. We believe that combining clinical examination with instrumental techniques can be useful to obtain information independent of the patient's ability for overt responses, and thus reduce the rate of misdiagnosis.

The aim of our study was to evaluate the importance of neurophysiologic techniques, in particular sleep recordings, in patients with prolonged DOCs by observing possible correlations between clinical evaluation and neurophysiologic variables.

2. Methods

2.1. Patients

Our study was conducted on 32 patients with severe brain injury whose ages ranged from 26 to 71 years (mean age, 52.94 ± 11.89 years). There were 27 patients who were diagnosed as being in a VS (mean age, 52.56 ± 12.32 years; CRS-R score, 4.89 ± 1.34) and 5 patients were in an MCS (mean age, 55.00 ± 10.12 years; CRS-R score, 9.00 ± 0.71). The diagnoses of VS and MCS were made according to currently accepted diagnostic criteria [9–11]. We recruited patients from different units (e.g., neurology, intensive care, intensive and long-term rehabilitation units) belonging to three different hospitals (''Sacro Cuore-Don Calabria'' Hospital in Negrar, Verona; ''Pineta del Carso'' Hospital in Aurisina, Trieste; and ''Santa Maria della Misericordia'' University Hospital in Udine). All data were collected using the same methods of acquisition and the same portable laptop system. DOCs were caused by traumatic brain injury (10 patients), cardiac or respiratory failure (15 patients), and hemorrhagic stroke (7 patients). The time between DOCs onset and the evaluation ranged between 3 months and 12 years (mean, 3.96 ± 3.37 years).

2.2. Procedure

Patients' inclusion criteria were confirmation of VS or MCS according to currently accepted diagnostic criteria [9–11], age between 18 and 75 years, Glasgow Coma Scale (GCS) score of $\leqslant$10, and Disability Rating Scale (DRS) score between 17 and 29. Clinical evaluation included a full neurologic examination and a clinical assessment with the GCS, the DRS, and the CRS-R. The clinical diagnosis was done by the local specialized personnel who observed and evaluated the patients on a daily basis. The CRS-R and the other clinical scales used for the behavioral assessment were applied right before and at the end of sleep recordings, always by the same investigator (SDB). Evaluations were consistent at different times. Among the clinical scales used we mainly used the CRS-R, as it is the most reliable and validated scale for the evaluation of patients with prolonged DOCs.

Neurophysiologic evaluation included 24-h polysomnography (PSG) and three evoked potentials (EPs), including somatosensory

Table 1
Demographic and clinical data.

Patient	Age (y)	Gender	Years between DOCs onset and registration	Etiology	DOCs level	GCS	DRS	CRS-R	Sleep-wake cycle	K-complexes	Spindles	REM sleep	BAEPs	SEPs	VEPs
1	26	M	6	Traumatic brain injury	VS	8	24	7	P	P	P	P	P	A	A
2	64	M	6	Cardiac failure	VS	6	28	2	P	P	A	P	P	A	P
3	64	M	7	Hemorrhagic stroke	VS	6	26	4	P	P	P	A	A	P	A
4	61	M	12	Traumatic brain injury	VS	6	26	6	P	P	P	P	A	P	P
5	46	M	2	Cardiac failure	VS	7	24	5	P	P	A	A	P	P	NR
6	70	M	1	Cardiac failure	VS	6	26	4	A	A	A	A	NR	NR	NR
7	37	W	3	Traumatic brain injury	VS	6	26	4	P	P	P	A	A	A	NR
8	37	W	1	Cardiac failure	VS	6	26	3	P	P	P	A	P	NR	A
9	41	W	1	Cardiac failure	VS	6	26	3	P	P	P	A	NR	NR	NR
10	55	M	3	Traumatic brain injury	VS	6	25	3	P	P	A	P	P	A	NR
11	61	M	0.3	Hemorrhagic stroke	VS	6	26	5	A	A	A	A	P	P	P
12	58	M	1	Cardiac failure	VS	8	24	6	P	P	P	A	A	P	P
13	50	M	1	Hemorrhagic stroke	VS	8	24	5	P	P	P	A	A	A	P
14	59	M	3	Traumatic brain injury	VS	8	24	5	P	P	P	A	P	P	P
15	71	W	9	Cardiac failure	VS	8	24	5	P	P	P	A	P	P	P
16	33	M	0.25	Hemorrhagic stroke	VS	8	24	6	P	P	P	A	A	P	P
17	52	M	5	Cardiac failure	VS	8	24	6	A	A	A	A	P	A	A
18	52	W	8	Cardiac failure	VS	8	23	7	P	P	A	A	A	A	P
19	51	M	5	Cardiac failure	VS	8	23	5	P	P	A	A	A	P	P
20	53	M	2	Traumatic brain injury	VS	9	22	6	A	A	A	A	A	NR	P
21	71	W	1	Cardiac failure	VS	6	26	4	P	P	P	A	P	P	P
22	65	M	3	Cardiac failure	VS	8	23	3	A	A	A	A	A	A	A
23	50	W	3	Hemorrhagic stroke	VS	6	26	5	P	P	A	A	P	P	P
24	40	M	12	Traumatic brain injury	VS	9	23	7	P	P	P	A	A	P	P
25	65	W	1	Respiratory failure	VS	8	24	5	P	P	P	A	A	P	A
26	50	W	10	Respiratory failure	VS	8	24	5	P	P	P	A	A	P	P
27	37	M	1	Traumatic brain injury	VS	8	24	6	P	P	A	A	P	P	A
28	43	M	6	Cardiac failure	MCS	10	21	8	P	P	P	P	P	P	P
29	46	M	3	Traumatic brain injury	MCS	7	22	9	P	P	P	P	P	A	NR
30	65	M	5	Hemorrhagic stroke	MCS	10	22	9	P	P	P	P	P	P	P
31	57	M	4	Traumatic brain injury	MCS	10	22	9	P	P	P	P	P	P	P
32	64	M	1	Hemorrhagic stroke	MCS	9	23	10	P	P	P	P	P	P	P

Abbreviations: y, years; M, man; W, woman; DOCs, disorders of consciousness; VS, vegetative state; MCS, minimally conscious state; GCS, Glasgow Coma Scale; CRS-R, Coma Recovery Scale-Revised; DRS, Disability Rating Scale; P, present; A, absent; REM, rapid eye movement; BAEP, brainstem auditory evoked potentials; SEP, somatosensory evoked potentials; VEP, visual evoked potentials; NR, not recorded.

EPs (SEPs), brainstem auditory EPs (BAEPs), and visual EPs (VEPs). The main demographic and clinical data can be found in Table 1.

The protocol was approved by the Ethics Committee of our hospital ("Santa Maria della Misericordia" University Hospital in Udine) and informed consent was obtained from the patients' legal representatives.

2.2.1. Sleep recordings

Sleep montage included 19 electroencephalogram channels with electrodes placed according to the 10–20 international system, two electrooculogram channels (right outer canthus and left outer canthus both referred to the left mastoid [M1]), one electromyogram channel (mylohyoid muscle), and one electrocardiogram channel. The impedance of recording electrodes was kept below 5 kΩ. The PSG and EPs were recorded at the patient's bedside with a portable laptop system (Micromed™ system MYOHANDY and HANDYEEG). The evaluation of sleep recordings was manually performed from the screen. The total duration of the recordings was 24 h. The same sleep expert (GLG) who was blind to patient's information manually analyzed all sleep recordings. We investigated the presence of sleep–wake cycle, sleep spindles, and K-complexes (indicators of nonrapid eye movement [NREM] sleep) and REM sleep. According to the *American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications* [12], each sleep element was classified as present, it was sufficient one ultradian cycle, and for REM sleep it had to be present at least once in 24 h.

2.2.2. EP recordings

BAEPs were recorded by stainless steel needle electrodes placed at the Cz area and at the ipsilateral and contralateral ear after 2000 monaural stimulations of 110-dB intensity. Low-pass frequency filter was set to 200 Hz and high-pass frequency filter to 2.5 kHz. The latencies and amplitudes of I, II, III, IV, and V waves were measured, as well as the interpeak interval of waves I–III and I–V. SEPs from right and left median nerves were recorded with stainless steel needle electrodes placed at Erb's point (referred to contralateral Erb's point), spinous process Cv7 (referred to anterior neck), C3' (referred to C4' and left Erb's point for the right side and vice versa for the left one). Pulse duration was 0.3 ms, stimulus rate was 2.7 Hz, low-pass frequency filter was set to 5 Hz, and high-pass frequency filter was set to 2 kHz. The N9, N13, P14, and N20 amplitudes and latencies were measured.

Visual processing was assessed by VEP for both eyes separately using flash stimulus. VEPs were recorded using a stainless steel needle electrode placed at Oz, referred to the frontal electrode at Fz. Low-pass frequency filter was set to 2 Hz and high-pass frequency filter to 200 Hz. The latencies and amplitudes of P100 waves were measured.

The analysis of the EP waveforms was performed with a visual inspection by two experts (SDB and SL). Evaluation of EPs was performed without knowledge of the clinical status of the patient. EPs were considered present if identifiable at least unilaterally. Independently of prolonged latencies or of reduced amplitudes, the following responses had to be clearly discernible to score an EP as present: wave V for BAEPs, N20 for SEPs, and P100 for VEPs. For technical, clinical, or ethical reasons not all data were collected from each enrolled patient. Namely it was not possible to record two BAEPs, four SEPs, and six VEPs.

2.3. Statistical analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed in percentage. We correlated clinical scores (CRS-R) with age categories, DOCs level, PSG patterns, and EPs. Comparisons between variables were performed using the Fisher exact test for categorical data and *t* tests or Mann–Whitney tests for parametric and nonparametric data, respectively. To identify an independent association between CRS-R scores and the different neurophysiologic tool analyzed, we performed a multivariate linear regression with forward stepwise selection including several demographic and clinical variables as confounders (i.e., age, gender, number of years from DOCs onset). Two-way interaction terms also were considered. The level of significance was defined at $P < .05$. Statistical analysis was performed using the SAS System version 9.3 software.

3. Results

The presence of EPs and each single sleep element was not significantly influenced by sex, age, DOCs etiology (e.g., posttraumatic vs other causes), and DOCs level (VS vs MCS). The only exceptions were for REM sleep and the simultaneous presence of all sleep elements were significantly more frequent in MCS than in VS patients (Fisher exact test: $P = .0009$ and $P = .0001$, respectively).

In all 5 MCS patients (100%) we found the presence of all sleep elements. All EPs were identifiable in 4 out of 5 patients, but VEPs were not recorded and the N20 SEP component was bilaterally absent in the fifth patient. Data from the 27 patients in VS are presented in Table 2. In those patients who showed sleep spindles (55.6%), the spindles appeared more clearly discernible in the central derivations (Fig. 1) without any topographic peculiarities. Among the 4 VS patients (14.8%) showing REM sleep (Fig. 2), we observed a well-represented cyclical appearance in 2 of the 4 patients. The hypnogram of these 2 patients is presented in Fig. 3, together with the hypnogram of a MCS patient and of a VS patient not showing REM/NREM alternation. In the remaining 2 VS patients REM sleep was found only once in 24 h and only for a few epochs. As indicated in the last row of the Table 2, it is noteworthy that only 7.4% of VS patients showed the simultaneous presence of all the examined sleep elements.

For subsequent analyses, clinical evaluation was compared using the CRS-R with neurophysiologic variables from all DOCs patients (both VS and MCS), as clinical misdiagnosis between VS and MCS can occur relying only on behavioral grounds, even including CRS-R.

Univariate analyses for each neurophysiologic tool are summarized in Table 3. For each sleep element, patients who showed presence of a sleep element had higher CRS-R scores compared to those who did not. In the case of REM sleep, the difference of the clinical scores had statistical significance ($P < .05$). In the same Table, 7 patients (5 MCS and 2 VS) who presented with all sleep elements had a CRS-R score of 8.29 ± 1.38, though 25 patients who lacked one or more of the normal sleep characteristics had a CRS-R score of 4.84 ± 1.46 ($P < .05$). Regarding EPs, patients who presented with each EP revealed higher clinical scores than those

Table 2
Evoked potentials and sleep recordings in 27 vegetative state patients.

	Absent (%)	Present (%)
BAEPs	52	48
SEPs	34.8	65.2
VEPs	31.8	68.2
Sleep–wake cycle	18.5	81.5
K-complexes	18.5	81.5
Spindles	44.4	55.6
REM sleep	85.2	14.8
All sleep elements	92.6	7.4

Abbreviations: BAEP, brainstem auditory evoked potentials; SEP, somatosensory evoked potentials; VEP, visual evoked potentials; REM, rapid eye movement.

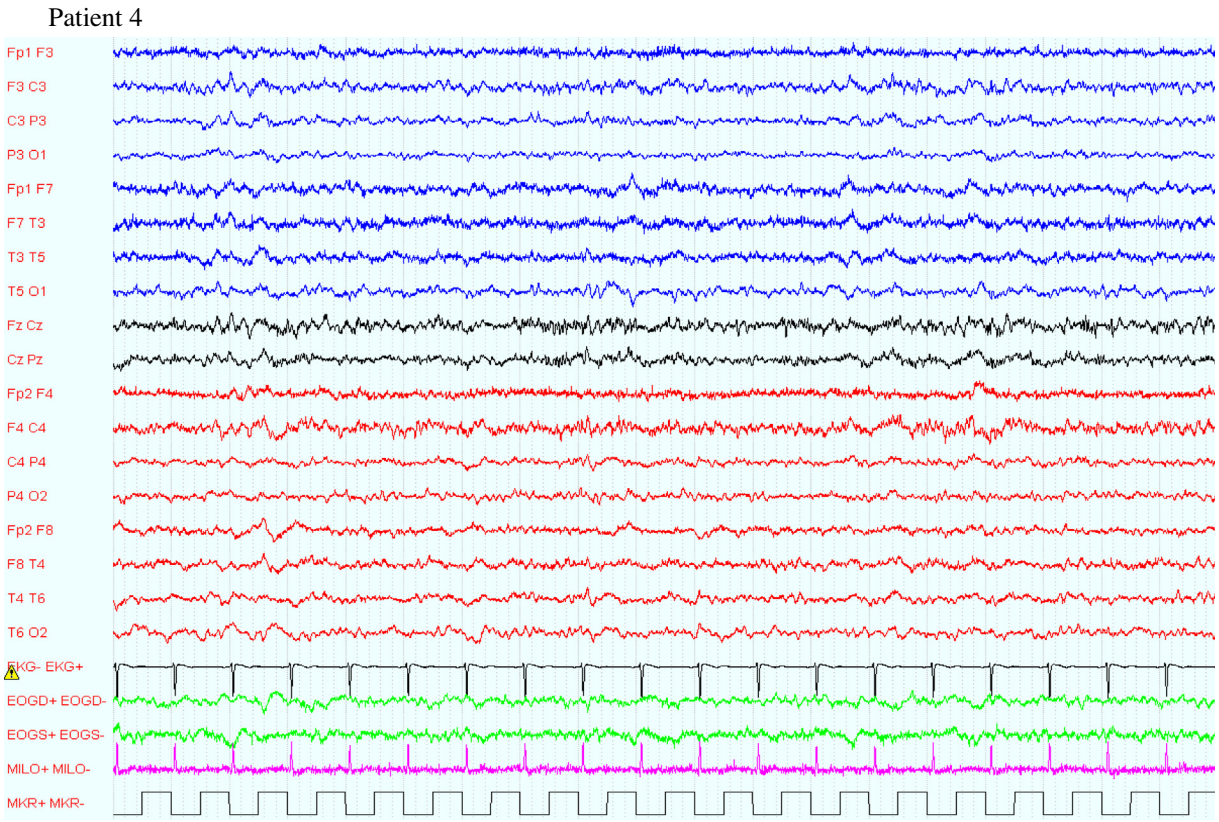

Fig. 1. Sleep spindles in a vegetative state patient.

who did not, even if there was no reported statistical significance ($P > .05$). Furthermore, considering the presence of two different EPs or of all EPs (only for patients in whom all the considered EPs had been recorded), there was only a trend for a higher scores at the clinical evaluation compared with patients lacking at least one of them; however, there was no statistical significance. Possible interaction and confounding by two or more variables predicting CRS-R were considered. In Table 4 mean CRS-R scores are displayed combined with the presence or absence of sleep spindles and REM sleep. Subjects with both sleep spindles and REM sleep had significantly higher CRS-R scores ($P < .0001$).

Results of the logistic multivariate regression analysis are summarized in Table 5. After adjusting for all other indicators, the simultaneous presence of REM sleep and sleep spindles, if taken together, more adequately correlated with CRS-R scores in DOCs patients ($P < .0001$). On the other hand, no significant associations were found between EPs and CRS-R scores.

4. Discussion

The aim of our study was to examine the importance of sleep recordings and EPs in DOCs patients, correlated to clinical evaluation. We paid particular attention to sleep recordings. The transition from coma to VS is defined by spontaneous eye opening and the reappearance of sleep–wake cycles. Five patients (15.6%) did not show a sleep–wake cycle; all of them were clinically found to be in a VS. In accordance with our results, Isono et al. [13] found that 4 VS patients (33%) with severe brainstem damage did not show a sleep-wake cycle. Therefore, further research is needed to determine if the presence of a sleep–wake cycle should continue to be included among the diagnostic criteria of VS. Collaterally, although we only performed a qualitative sleep analysis, sleep appeared more dispersed in VS than MCS patients in whom it was more consolidated during the night.

The presence of K-complexes was of little importance when considered as a sleep element, as they presented in the majority of patients (84.3%). Compared with K-complexes, sleep spindles showed a higher correlation with clinical scores, even though they did not show statistical significance. In the literature, even if the presence of sleep spindles in comatose patients did not always indicate a positive outcome, their absence was associated with a poor outcome [14]. REM sleep was found in 9 patients (28.1%). REM sleep appeared to be the one sleep element that most adequately correlated with clinical scores, as it was the only one that achieved statistical significance.

After adjusting for other variables and when we considered REM sleep together with sleep spindles, this association was even more significant. Therefore, the simultaneous presence of well-structured REM-NREM elements in our series correlated with the highest clinical scores in DOCs patients. Subjects showing all sleep elements had significantly higher CRS-R scores than those lacking one or more sleep element. After we considered different levels of consciousness in DOCs, a clear distinction was found in sleep recordings. All the sleep elements were present in 5 MCS patients (100%) but only in 2 VS patients (7.4%). This difference was statistically significant, particularly in REM sleep (100% in MCS vs 14.8% in VS patients). Therefore, PSG recordings may be helpful for the clinician to differentiate between VS and MCS patients.

In healthy volunteers REM sleep has been linked to dreams, emotional content, vivid visual imagery, and information reprocessing during sleep [15]. In DOCs patients, especially those in a clinically VS, REM sleep reveals possible persistence of brain activities. In the context of limited resources, the detection of REM sleep in VS patients could be used as an indicator for selecting

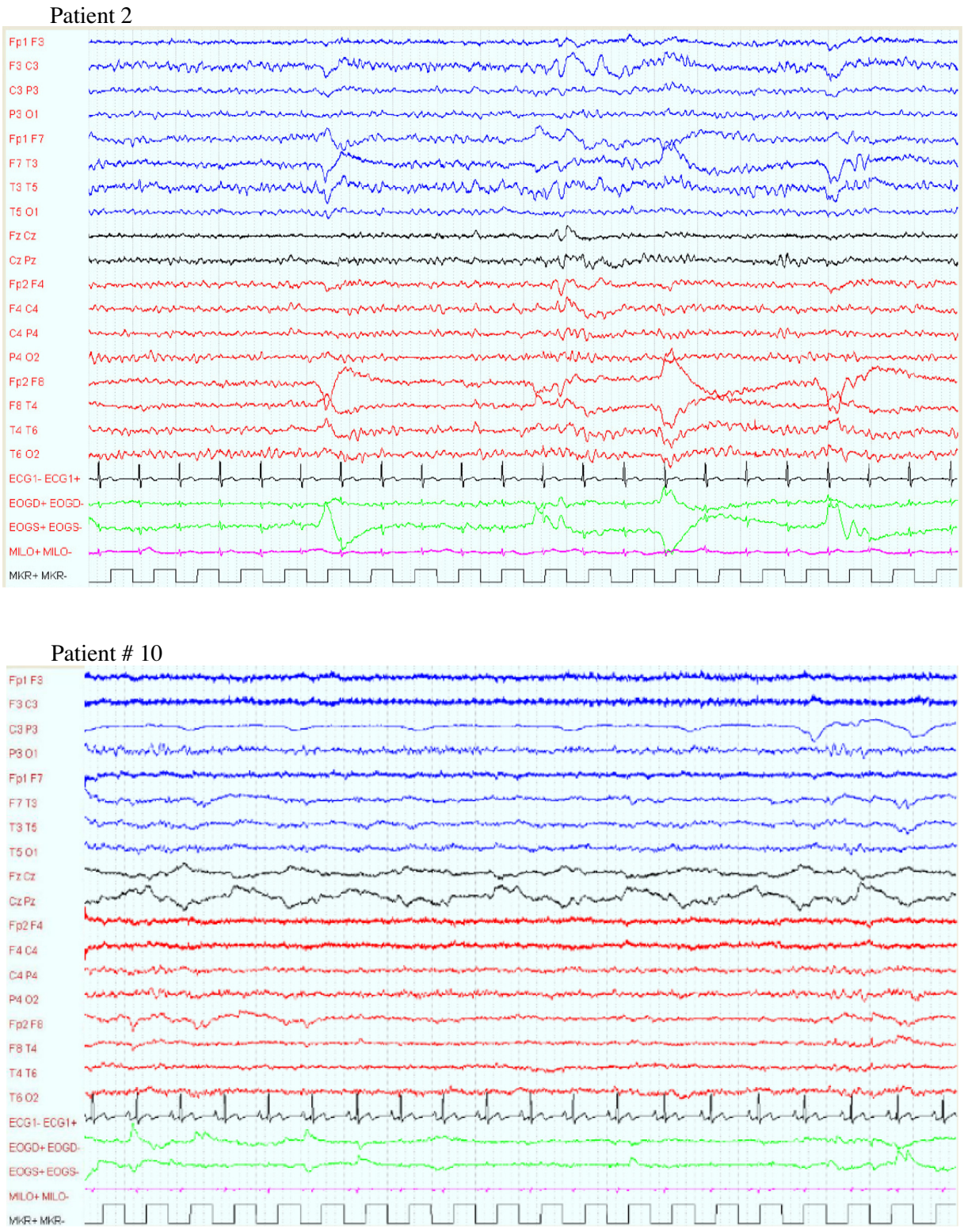

Fig. 2. Rapid eye movement sleep in two vegetative state patients.

patients to investigate with functional neuroimaging, as well as to submit to extensive cognitive rehabilitation. It would not be surprising if these patients would benefit from modern imaging techniques used to detect signs of residual hidden consciousness, of which there currently is no evidence on pure clinical grounds. Our findings are partially in accordance with those of Landsness et al. [16], in which all MCS patients showed an alternating NREM/REM sleep pattern, though no slow–wave sleep or REM sleep stages could be identified in VS patients.

Most of the existing literature reports spindling activity and REM changes related to recovery from coma. Different studies showed the presence of sleep patterns as a reliable prognostic marker both for survival and functional recovery in comatose patients [17,18]. In contrast, the absence of REM sleep and sleep patterns is

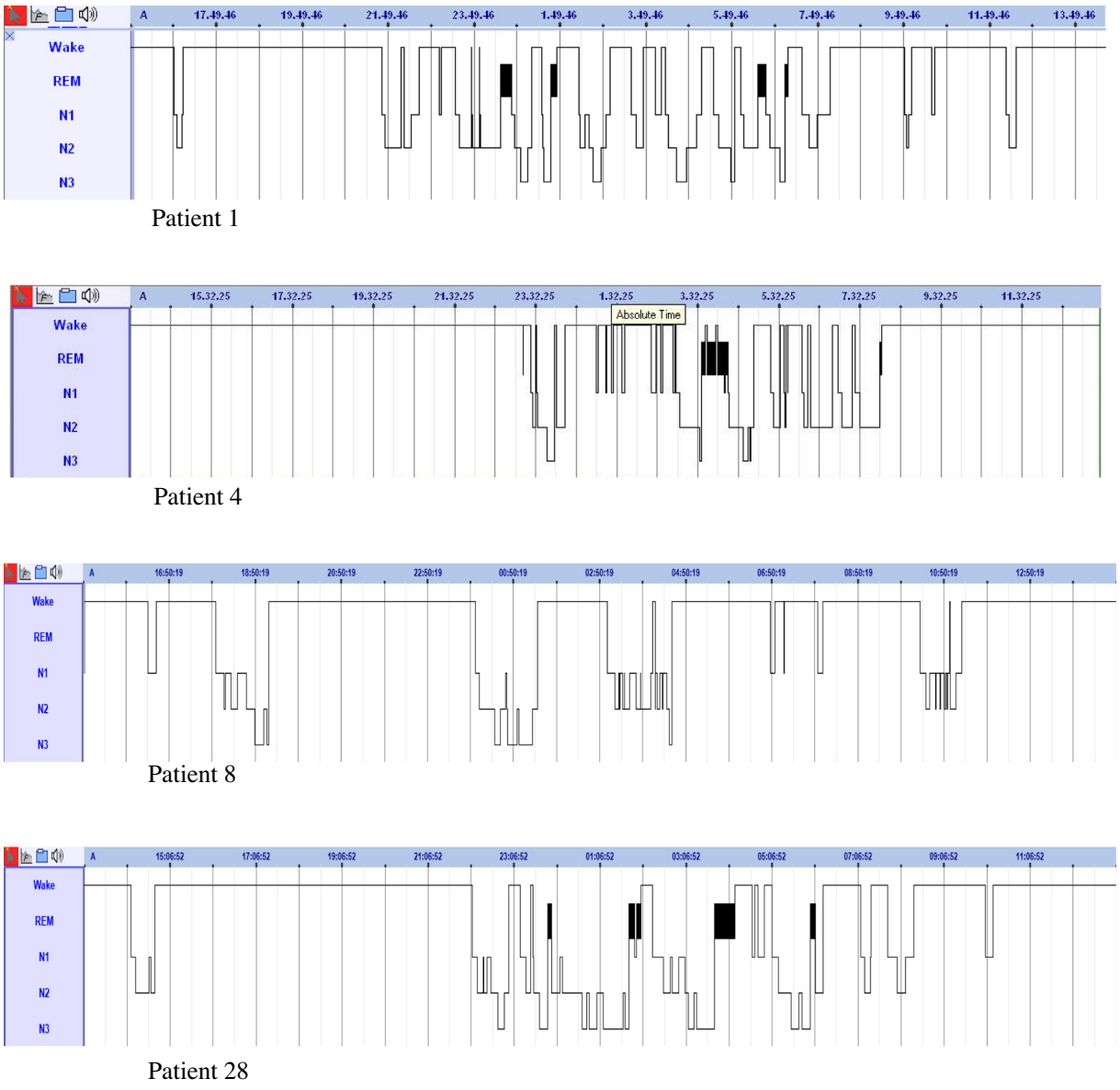

Fig. 3. Sleep hypnogram in two vegetative state (VS) patients showing rapid eye movement (REM) sleep (patient 1 and 4), in a VS patient not showing REM or non-REM sleep alternation (patient 8), and in a minimally conscious state patient (patient 28).

considered in different studies as an unfavorable prognostic sign [19]. Valente et al. [17] found that the presence of organized sleep patterns but not GCS was highly predictive of better outcomes in posttraumatic comatose patients. Only few studies have evaluated the prognostic significance of sleep in patients with prolonged disorders of consciousness. D'Aleo et al. [20] found evidence of spindles in 11 out of 20 traumatic and 3 out of 10 hypoxic VS patients. In addition, the authors showed an increase of spindle density from 5 to 12 per minute, paralleling the clinical recovery of traumatic patients. Compared to a healthy control group, Giubilei et al. [21] found that only minor sleep alterations were present in 9 traumatic VS patients with a positive outcome, and no sleep patterns were found in one permanent VS patient. It should be emphasized that some of the patients who were previously reported as VS by the older literature may actually be MCS, as the latter was established as a separate entity only in 2002 [10].

In our series, EPs showed a weaker correlation with clinical evaluation compared to sleep recordings. Patients with each EP always had higher clinical scores compared with those who had not, though the result was not statistically significant. Even considering the simultaneous presence of two or all EPs, we did not find significance. Moreover, no significant associations were found between EPs and CRS-R scores in the multivariate analysis. Like sleep, EPs have been evaluated more in comatose patients rather than in patients with prolonged DOCs. BAEPs have a prognostic value of poor outcome in comatose patients when they are considered as abnormal, provided that lesions to the peripheral auditory system have been ruled out [22]. No prognostic value is attached to their normality.

Regarding SEPs, the bilateral abolition of the cortical N20 SEP component is related to a poor outcome in postanoxic patients, defined as death or survival in VS patients with 100% specificity. Following traumatic brain injury, the predictive value for unfavorable outcomes is 98.5% when focal injuries likely to abolish SEP cortical components have been excluded [23,24]. In contrast, the presence of normal SEPs in comatose patients appeared to have a favorable predictive value for recovery [25,26]. However, event-related potentials (ERPs) such as P300 and mismatch negativity (MMN)

Table 3
Coma Recovery Scale-Revised scores and presence of different neurophysiologic variables.

	CRS-R score ± SD	*P* value
BAEPs	Absent 5.31 ± 1.18	.609
	Present 5.94 ± 2.38	
SEPs	Absent 5.11 ± 2.31	.315
	Present 6.05 ± 1.75	
VEPs	Absent 4.86 ± 1.57	.215
	Present 6.05 ± 1.93	
BAEPs + VEPs	Absent 5.44 ± 1.26	.748
	Present 6.20 ± 2.62	
BAEPs + SEPs	Absent 5.29 ± 1.76	.291
	Present 6.45 ± 2.11	
VEPs + SEPs	Absent 5.00 ± 1.73	.210
	Present 6.33 ± 1.84	
All evoked potentials	Absent 5.33 ± 1.45	.378
	Present 6.67 ± 2.29	
Sleep–wake cycle	Absent 4.80 ± 1.30	.460
	Present 5.67 ± 2.06	
K-complexes	Absent 4.80 ± 1.30	.460
	Present 5.67 ± 2.06	
Spindles	Absent 4.75 ± 1.48	.160
	Present 6.00 ± 2.10	
REM sleep	Absent 4.96 ± 1.15	<.05
	Present 7.00 ± 2.83	
All sleep elements	Absent 4.76 ± 1.30	<.05
	Present 8.29 ± 1.38	

Abbreviation: CRS-R, Coma Recovery Scale-Revised; SD, standard deviation; BAEP, brainstem auditory evoked potentials; SEP, somatosensory evoked potentials; VEP, visual evoked potentials; REM, rapid eye movement.

Table 4
Coma Recovery Scale-Revised scores and interaction between sleep spindles and rapid eye movement sleep.

	No. of patients	CRS-R score ± SD
Spindles absent and REM sleep absent	10	5.20 ± 1.14
Spindles present and REM sleep absent	13	4.77 ± 1.17
Spindles absent and REM sleep present	2	2.50 ± 0.71
Spindles present and REM sleep present	7	8.29 ± 1.38
		$F = 18.77$; $df = 3$; $P < .0001$

Abbreviations: No., number; CRS-R, Coma Recovery Scale-Revised, CRS-R; SD, standard deviation; REM, rapid eye movement.

Table 5
Independent predictors of Coma Recovery Scale-Revised in disorders of consciousness patients.

Variable	T score	*P* value
Age (y)	0.19	.8510
Gender	−0.90	.3801
Years from DOCs onset	−0.28	.7842
DOCs etiology (posttraumatic vs other etiologies)	−0.27	.7903
Sleep–wake cycle/K-complexes*	0.83	.4176
Spindles	−0.97	.3448
REM sleep	−2.90	.0089
Spindles and REM sleep	5.10	<.0001
BAEPs	−0.60	.5553
SEPs	−0.38	.7103
VEPs	−0.04	.9703

Abbreviations: y, years; DOC, disorders of consciousness; REM, rapid eye movement; BAEP, brainstem auditory evoked potentials; SEP, somatosensory evoked potentials; VEP, visual evoked potentials. Coma Recovery Scale-Revised predictors ($R^2 = 073$; $F = 22.95$).

* Considered together because present in the same patients.

are considered to be superior to stimulus-related EPs in predicting awakening from coma [27]. In effect, the presence of ERPs can reveal some level of residual cognitive processing. Fischer et al. [28] affirmed that the presence of MMN was a predictor of awakening and precluded comatose patients from moving to a permanent VS. There are studies that describe a clear difference in ERP responses among VS and MCS patients, considering ERP as a valid tool for differentiating these two conditions [29,30]. However, this difference was not found in other studies [31,32]. In particular, Fischer et al. [31] found that the presence of cognitive components (MMN and nP3) was scarce and not statistically different in MCS and VS patients in a study regarding permanent VS or MCS patients (i.e., a population similar to our sample) [31]. Further studies are needed to compare the ability of ERPs and sleep recordings in differentiating VS and MCS patients.

In a recent study, Ragazzoni et al. [33] demonstrated that the recording of transcranial magnetic stimulation EPs (TEPs) can be helpful to differentiate VS from MCS patients. Cortical reactivity and connectivity was severely impaired in all VS patients, whereas the TEPs were preserved but with abnormal features in most MCS patients. TEPs can be recorded at the patient's bedside without requiring patient's collaboration and can add valuable information to the clinical assessment of DOCs patients.

4.1. Limitations

An important limit of our study was that we evaluated patients in stabilized conditions. It would have been interesting to examine sleep recordings in our patients from the acute stage of DOCs. Because CRS-R relies on two single time point examinations, whereas PGS relies on 24-h recordings, the observation period of PSG is likely to be more useful. We are aware that this limitation is intrinsic to the method, and we cannot fully exclude the possibility that sleep recordings may have a greater statistical power in observing a phenomenon instead of revealing otherwise hidden thalamocortical mechanisms. Another unresolved limitation is that at our time sleep stage criteria are undefined in DOCs, and therefore criteria need to be explicitly defined to establish sleep staging [20]. Finally, a total of 12 EPs were not performed, which may have decreased the power of the EPs results.

4.2. Final considerations

Clinical examination remains the gold standard in DOCs evaluation. However, despite the improvements obtained with the clinical scales, especially CRS-R, it is challenging to differentiate reflex or automatic motor behavior from movements indicating signs of consciousness at the patient's bedside; hence some MCS patients might have been misdiagnosed as being in a VS [34]. The distinction between VS and MCS is important for prognosis, treatment decisions, resource allocation, and medicolegal judgments [35]. Comparing long-term functional outcome, Luauté et al. [36] found that one-third of patients in MCS improved more than 1 year after coma onset in contrast to patients in VS. The authors emphasized the need to define reliable boundaries between VS and MCS using repeated clinical evaluations and all imaging and neurophysiologic tools currently available.

In our study, PSG proved to be a more adequate tool than EPs for the neurophysiologic assessment of patients with prolonged DOCs. The main contribution to better clinical scores was determined by the concomitant presence of REM sleep and sleep spindles. Furthermore REM sleep may reveal the presence of residual conscious activities in patients clinically considered to be in a VS. Therefore, PSG can be helpful for the differential diagnosis between a VS and MCS, providing additional prognostic information. Although longitudinal studies using 24-h PSG in these patients are lacking, it is reasonable to think that 24-h PSG might become a useful prognostic marker in DOCs patients. In this case, sleep recordings should begin in the first stages in the intensive care units.

5. Conclusion

If a multimodal approach represents the best way to assess patients with prolonged DOCs, PSG may be considered as an inexpensive, noninvasive, and easy-to-perform examination to provide fundamental information to support the clinical evaluation and should be performed as part of the routine assessment in DOCs patients.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.09.026.

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